2026 ESMO TAT

Targeted Anticancer Therapies

A Phase 1 Trial of TOS-358, a Covalent PI3Kα inhibitor, in Patients with HR+/HER- Metastatic Breast Cancer (MBC), Endometrial Adenocarcinoma (EA), & Head/Neck Squamous Cell Carcinoma (HNSCC)

Phase 1a Results

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ESMO

DECLARATION OF INTERESTS

Disclosures:

- Consulting: Pfizer/Arvinas, Eli Lilly, Novartis, Incyclix, Araris, Guardant Health
- Travel: Totus Medicine, Eli Lilly, Pfizer
- Research Funding (to Dana-Farber Cancer Institute): Cardiff Oncology

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Background

PI3Kα-mutant cancer represents one of the most significant unmet needs in oncology

PI3Kα is the Most Frequently Mutated Oncogene

>125,000 patients/year

- Mutated in ~15% of all cancers: 30-40% ER+ Breast, 49% Endometrial, 22% Bladder, 28% Colorectal cancers

Limitations of Current Treatment Options

Current treatment options do not cover all PI3Kα mutations

- Non-covalent inhibition of PI3Kα results in peak -to-trough variability of inhibition from ~80% to ~35% while consistent >90% coverage is required for optimal efficacy and durability. Only a covalent inhibitor can keep the consistent pressure on target at doses with a tolerable AE profile
- High-grade and/or serious toxicities make combination therapy challenging, especially if overlapping with backbone CDK4/6i

TOS-358

A covalent, pan-mutant, PI3Kα-selective inhibitor

- Exhibits sustained monotherapy activity with a class leading safety profile
- Pan-mutant (incl. acquired resistance mutations) coverage with target inhibition >90% at clinical doses
- Phase 1a completed; results presented reflect Phase 1a data. Ph1b ongoing.

Sources: Trinity Life Sciences, cBioPortal, Cancer Genetics, J Kim et al (Sept 2025)

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TOS-358: Phase 1a Clinical Trial Design

Ph 1a – Safety, Dose Optimization & Efficacy

All comers

Safety, PK, PD & Dose Finding



N = 82

Doses & Schedules Explored:
BID dosing: 2 mg -15 mg

Efficacy expansion cohort 5-10 mg BID

Efficacy expansion cohort



N = 20

[Additional doses & schedules were explored but are not the focus of todays presentation]

Enrollment criteria:

+ PI3Kα mutations with focus on breast cancer; also includes HNSCC and endometrial adenocarcinoma
+ ≤1 prior line of chemotherapy
+ ≤3 prior lines of metastatic therapy
+ Allowed to remain on fulvestrant if already on tx
+ Fasting blood glucose ≤140 mg/dL
+ Hb A1c ≤7%
+ **Allows prior PI3K/AKT/mTOR therapy**

Heavily pre-treated patient population:

+ 40% on 4L post-met
+ 35% post prior PI3K treatment
+ No mandatory prophylaxis for any AE

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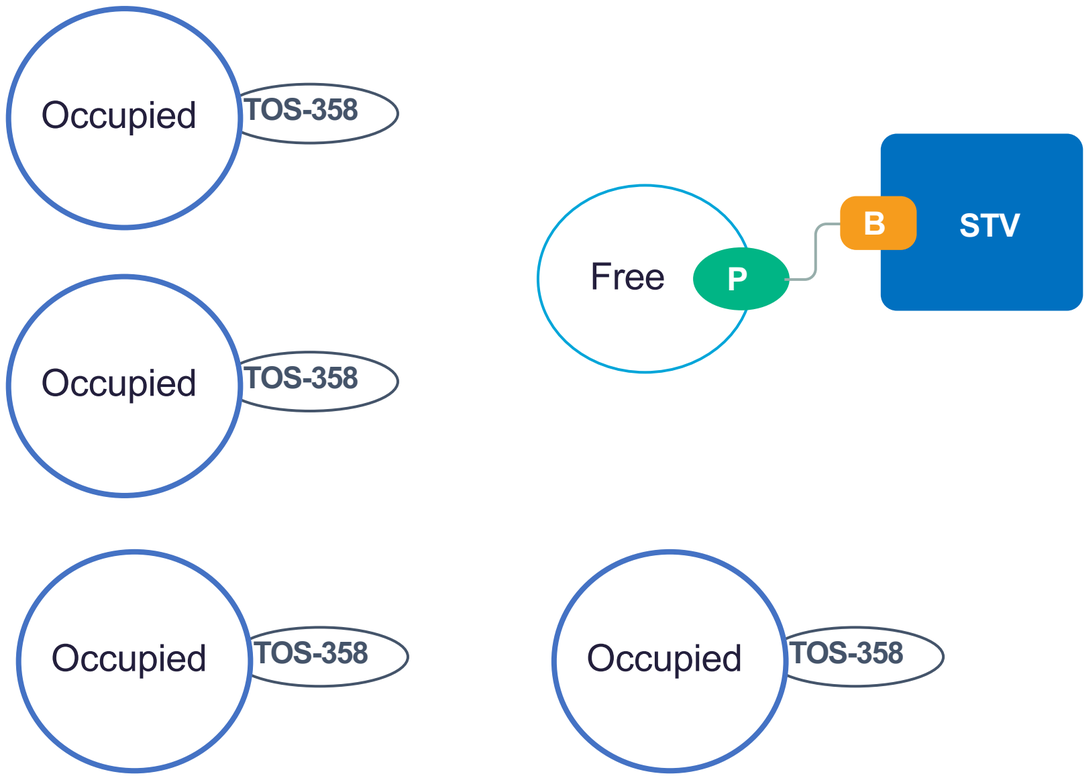
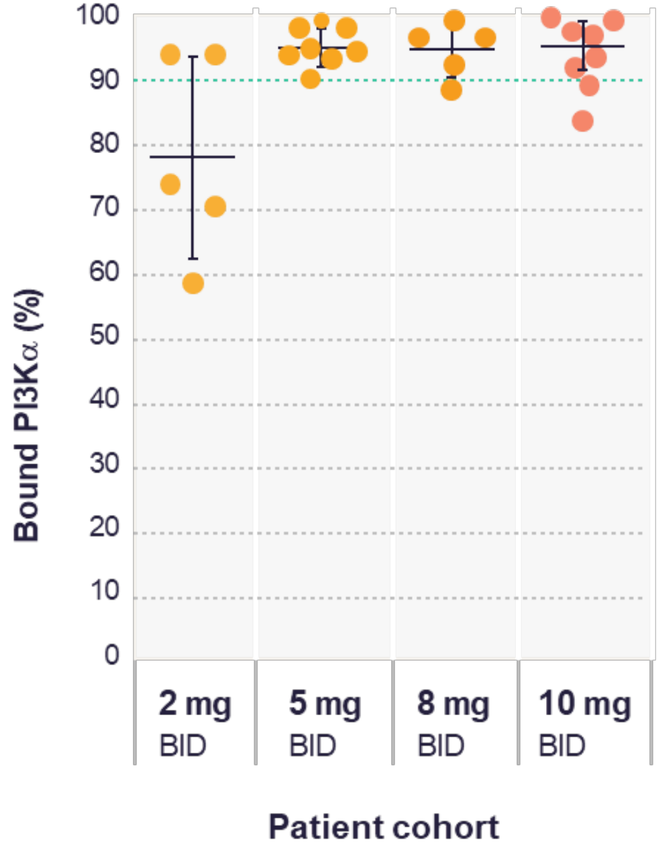
Saturating Target Engagement

PBMC-Based Target Engagement & Pharmacodynamic Assay

Pharmacodynamic assay detects occupied, unoccupied, and total PI3Kα



PI3Kα PBMC target engagement Samples at dosing trough



Ref: A Streptavidin Mass Shift Assay for Rapidly Quantifying Target Occupancy by Irreversible Inhibitors, Labenski, Biochemistry 2021, 60, 2915−2924

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Baseline Demographics & Disease Characteristics

Patients included in the safety analysis & dosed at 5, 8, 8→10, or 10 mg BID

TOS-358 (Total N=54)					
Characteristic	5 mg BID (N=22)	8 mg BID (N=15)	8 to 10 mg BID (N=13)	10 mg BID* (N=4)	Total (N=54)
Age, year, median (range)	58 (37-73)	61 (39-82)	61 (39-78)	65.5 (47-77)	60.5 (37-82)
Female sex, n (%)	17 (77.3)	12 (80.0)	11 (84.6)	4 (100)	44 (81.5)
Race/ethnic group, n (%)					
White	19 (86.4)	12 (80.0)	12 (92.3)	4 (100)	47 (87.0)
Asian	2 (9.1)	0	0	0	2 (3.7)
American Indian or Alaska Native	1 (4.5)	0	0	0	1 (1.9)
Black or African American	0	1 (6.7)	0	0	1 (1.9)
Unknown/Not Reported	0	2 (13.3)	1 (7.7)	0	3 (5.6)
ECOG PS Score, n (%)					
0	8 (36.4)	9 (60.0)	7 (53.8)	4 (100)	28 (51.9)
1	14 (63.6)	6 (40.0)	6 (46.2)	0	26 (48.1)
Prior Lines of Therapy, median (range)	3.0 (2-8)	3.0 (1-6)	4.0 (1-6)	3.0 (2-5)	3.0 (1-8)
Post Metastic Therapy, median (range)	3.0 (1-5)	2.0 (1-6)	2.0 (1-3)	2.0 (1-3)	2.0 (1-6)
PI3K mutation Type					
Helical	6 (27.3)	4 (26.7)	4 (30.8)	3 (75.0)	17 (31.5)
Kinase	11 (50.0)	5 (33.3)	4 (30.8)	1 (25.0)	21 (38.9)
Other	4 (18.2)	3 (20.0)	3 (23.1)	0	10 (18.5)
Multiple	1 (4.5)	3 (20.0)	2 (15.4)	0	6 (11.1)

Database as of 04-Jan-2026
Table 1.2

** Only HR+/HER2- BC, HNSCC, or Endometrial Cancer are included*

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Class Leading Safety Profile – any TEAE ≥5% & All Grade 3-5

TOS-358 (Total N=54)						
Related TEAEs	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
HYPERGLYCAEMIA (1x insulin)	38 (70%)	8 (15%)	26 (48%)	2	0	0
HYPERGLYCAEMIA (>1 insulin dose)				2	0	0
FATIGUE	10 (19%)	6 (11%)	3 (6%)	1	0	0
DECREASED APPETITE	7 (13%)	3 (6%)	4 (7%)	0	0	0
DIARRHOEA	7 (13%)	5 (9%)	2 (4%)	0	0	0
ASTHENIA	5 (9%)	2 (4%)	3 (6%)	0	0	0
DYSPEPSIA	4 (7%)	3 (6%)	1 (2%)	0	0	0
NAUSEA	8 (15%)	6 (11%)	2 (4%)	0	0	0
WEIGHT DECREASED	5 (9%)	2 (4%)	3 (6%)	0	0	0
LYMPHOCYTE COUNT DECREASED	1 (2%)	0	0	1	0	0
HYPOKALEMIA (being queried)	1 (2%)	0	0	1	0	0
METABOLIC ACIDOSIS	1 (2%)	0	0	1	0	0

Database as of 04-Jan-2026
Table 14.1

TOS-358 has class leading safety:

+ No bone marrow toxicity
+ No hepatic toxicity
+ No renal toxicity
+ No ocular symptoms
+ No rash
+ No stomatitis
+ No G3 diarrhea (13% G1-2)
+ Manageable hyperglycemia with only 2 patients requiring ongoing insulin

  On-target effect that is predictable & controllable

+ Doses providing ~95%+ target inhibition (5 or 8 mg BID; 10 mg BID efficacy evaluable)
+ As ‘n’ increases safety profile is stable

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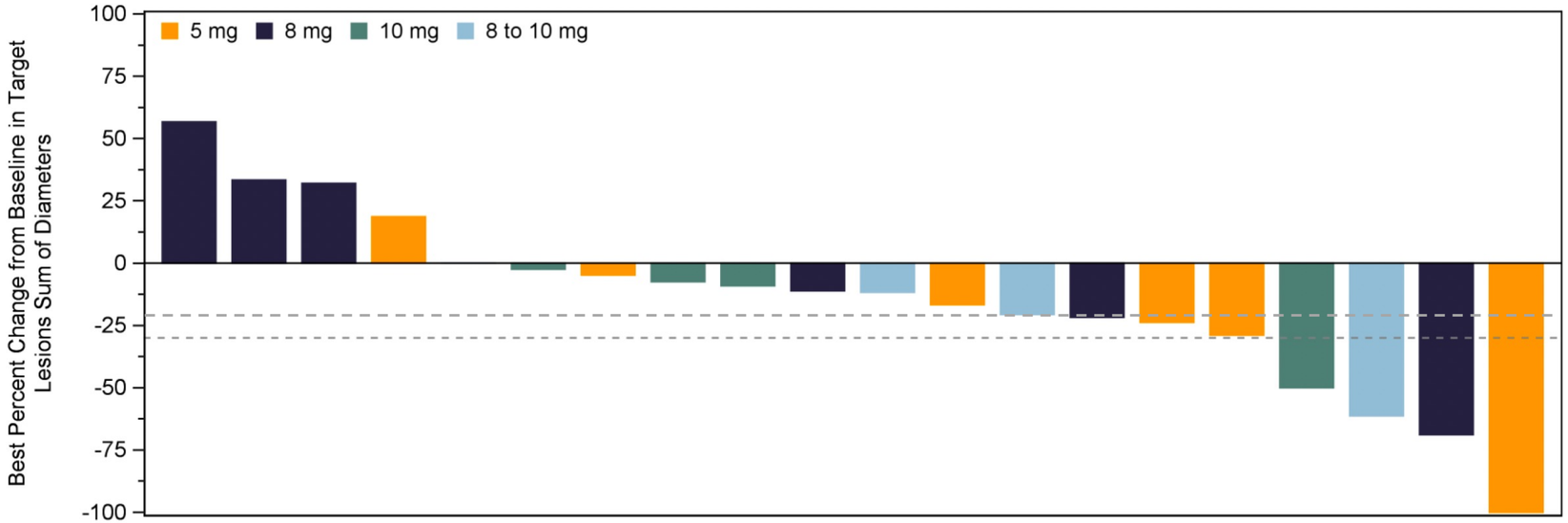
TOS-358: Demonstrates Clinically Meaningful Disease Control

Excellent Safety & Tolerability: 0% Liver Tox, Renal Tox, Stomatitis, Rash



BOR	PD	PD	PD	PD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	PD	PR	PR	CR
DoE (Weeks)	9	9	10	9	15	48	40	18	66	33	12	39	12	27	16	41	9	12	48	25
Cancer Type	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	H	B	B	E	H
Helical/Kinase/Other	H/O	H/O	K	H	H	H	K	K	H	K	H	K	K	H	K/O	O	H	K	K	H
Line of Met Tx	2	2	2	1	1	2	3	2	3	3	3	1	3	3	1	1	1	1	3	3
Prior PI3K/AKT/mTORi		Y(P)					Y(T)	Y(P)	Y(T)	Y(P)			Y(P)	Y(T)						

Efficacy evaluable cohort: BC, EA, HNSCC; E345,E542, E545, H1047; 1st on tx scan at 8wk
Database as of 04-Jan-2026

Clinical Benefit Rate (CBR) CBR = CR+PR+SD ≥24wks	**50%**
Durability ≥24 weeks on drug	**45%**
Disease Control Rate (DCR) **Best response** ≥ SD	**75%**
Stable Disease (SD)	**60%**
Tumor response -20%	**40%**
Tumor response -30% (ORR)	**15%**

Database as of 04-Jan-2026

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TOS-358: Excellent Durability with 45% of Patients on 24+ weeks

Sustained Tumor Control with a Favorable & Predictable Tolerability Profile

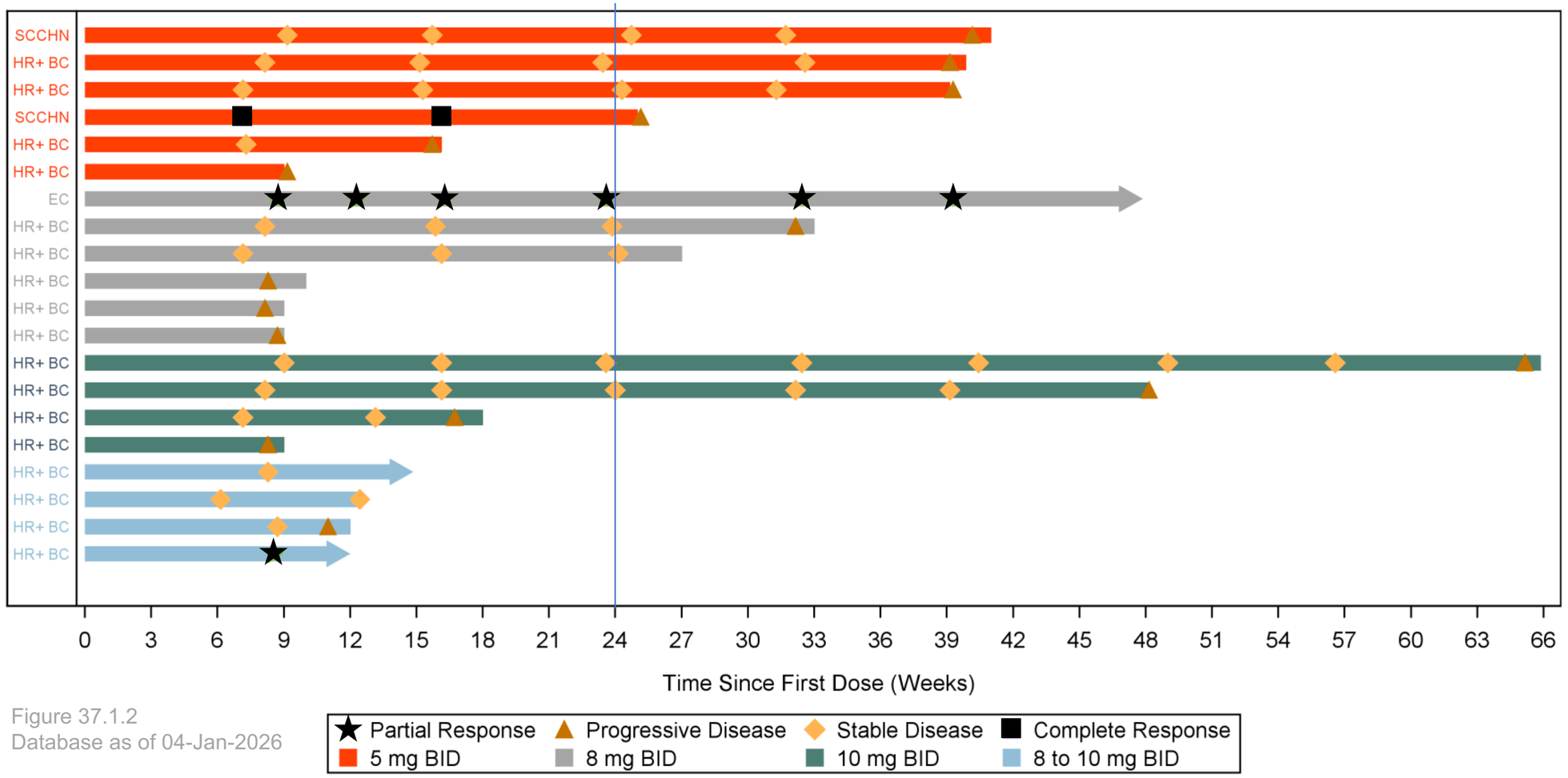

Figure 37.1.2
Database as of 04-Jan-2026

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BC Patients Who Progressed on Prior PI3Kα/AKT/mTOR (PAM)

A Path to Rescue PAM Progressing Patients, Delay Cytotoxic Chemotherapy & Overcome PAM Intolerance

Subject ID	Prior PI3Kα/AKT/mTOR		TOS-358 Treatment	
	Therapy	Best response	Best Response (tumor volume)	Duration of treatment
A	everolimus	SD	**SD (-11%)**	**33 weeks**
B	alpelisib everolimus	PD PR	PD (-3%)	8 weeks
C	everolimus	PD	PD (33%)	9 weeks
D	everolimus	Not available	**SD (-8%)**	**18 weeks**
E	LOXO-783	SD	**SD (-21%)**	**12 weeks**
F	everolimus	PD	**SD (-13%)**	**17 weeks+**

Patients who Progressed on prior PAM Therapy

Patients Intolerant to PAM Therapy

Subject ID	Prior PI3Kα/AKT/mTOR		TOS-358 treatment		
	Therapy	Duration of Tx	Dose	Best response (tumor vol)	Duration of treatment
G	alpelisib	**8 weeks intermittent**	5 mg BID	**SD (0%)**	**40 weeks**
H	alpelisib	**8 weeks**	8 mg BID	**SD (-22%)**	**27 weeks ***
I	everolimus	**10 weeks**	10 mg BID	**SD (-9%)**	**66 weeks**

*patient died of unrelated event with tumor controlled

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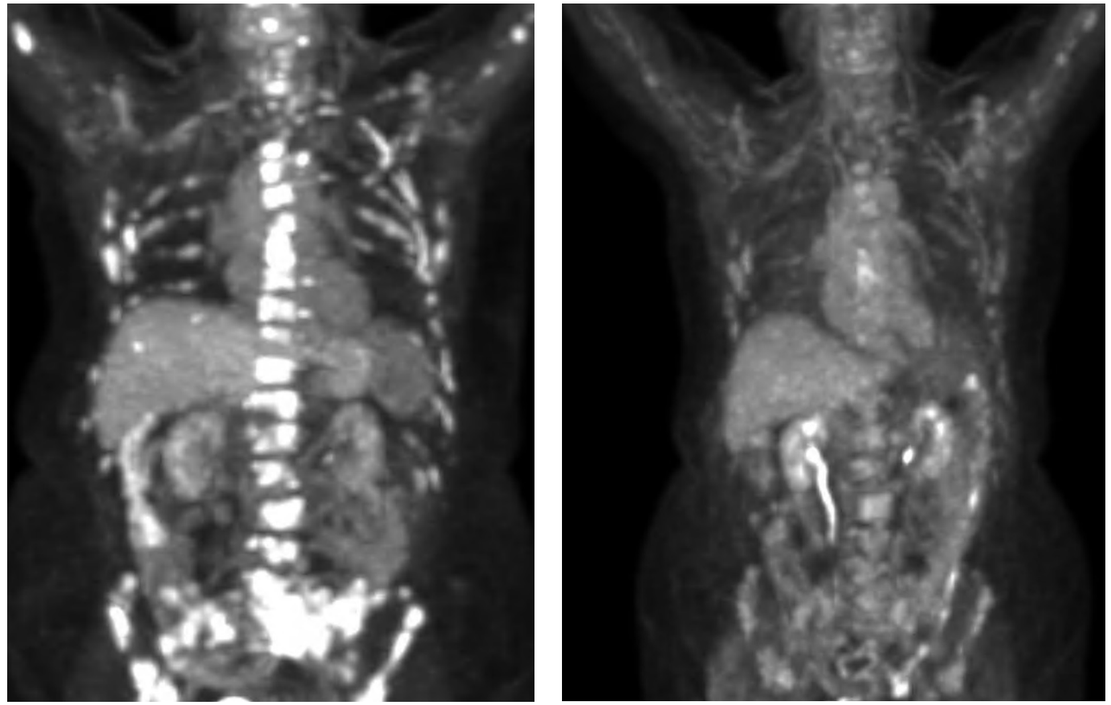
PET-CT Response in breast cancer patient with PI3Kα mutation

- **Patient Background**
  - + 72-year-old female; HR+ HER2- breast cancer
  - + Initial diagnosis 2006;
    metastatic disease diagnosis in 2021
  - + PI3Kα mutation: H1047K/G106V

- **Prior Therapies & Corresponding Best Response**
  1. Cytoxan/Taxotere | not available
  2. Anastrozole | not available
  3. Exemestane/palbociclib | PD
  4. Abemaciclib/letrozole | PD

- **TOS-358 Treatment & Response**
  - Treated with **TOS-358 at 8 mg BID + Fulvestrant**
  - **Treatment Ongoing**
  - **RECIST response SD (-20% target lesion, skin)**



Baseline | 8 weeks

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Conclusion

Durable Tumor Control with Excellent Tolerability in PIK3CA-Mutant Cancers

- **Efficacy:** The covalent, pan-mutant, selective TOS-358 demonstrates strong and durable activity, with **75% DCR, 50% CBR**, and clinically meaningful disease control in PAM-resistant (67%, 4/6) and PAM-intolerant (100%, 3/3) patients.
- **Durability:** 45% of patients in the Phase 1a efficacy cohort remain on treatment for ≥ 24 weeks, indicating improved durability relative to class benchmarks
- **Safety & Tolerability**: Class-leading safety profile with no bone marrow, hepatic, ocular, or dermatologic toxicities, no stomatitis, no GR ≥ 3 diarrhea and only 4% G2, and manageable hyperglycemia (3.6%, 2/54 patients requiring ongoing insulin)
- **Overall:** These data support a predictable, controllable on-target effect with sustained efficacy and favorable tolerability, enabling prolonged treatment
- **Ongoing study**: Phase 1b expansion, in doublet (TOS-358 + Fulvestrant) and triplet (TOS-358 + Fulvestrant + CDK4/6i) combinations, is currently enrolling patients with HR+/HER- breast cancer (NCT05683418)

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